REMARKS

The Final Office Action mailed May 23, 2002 has been received and reviewed. Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 are pending in the application. All stand rejected. Applicants propose to amend claims the application as set forth herein. Claims 1, 4-18, 20, 24, 26, 41 and 43 are to be cancelled. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

I. Double Patenting

The Final Office Action indicated that if claim 5 were found allowable, claims 6-8 and 41 would have been objected to under 37 C.F.R. § 1.75 as being substantial duplicates thereof. Claims 5, 6-8 and 41 have been cancelled rendering the double patenting objections moot.

II. Claim Objections

Claim 10 was objected to under 37 C.F.R. § 1.75(c) as being of improper dependent format. Claim 10 has been cancelled rendering the objection moot.

III. 35 U.S.C. § 112, Second Paragraph

Claims 2, 25, 37-40 and 42

Claims 2, 25, 37-40 and 42 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point and distinctly claim the subject matter which applicants regard as the invention. Applicants propose to amend claims 2, 38-40 and 42, and partially in view of the amendments respectfully request the rejections be withdrawn.

Independent claim 2 and claims 37-40 and 42 depending therefrom are directed to a recombinant adenovirus with a significantly reduced tissue tropism for liver cells, and independent claim 25 is directed to an adenovirus capsid with a significantly reduced tissue tropism for liver cells. The Final Office Action indicates that it is unclear to what extent the reduced tissue tropism between wild type adenovirus 5 and chimeric adenovirus for liver cells is "significant."

It appears that the Examiner is misunderstanding the data in Table II by comparing the results for lung and kidney cells, not just liver cells. Table II on page 47 of the specification

indicates the difference in luciferase activity between samples from liver cells when the control Ad5 is used and when the recombinant adenoviruses of the present invention are used. As illustrated on the top line of Table II which corresponds to data for liver cells, the counts decrease from 740045 in control Ad5 adenovirus, to reduced counts of 458, 8844, 419 and 2033 in recombinant adenoviruses Fib 12, Fib 16, Fib 28 and Fib 40-L, respectively. The counts for the recombinant adenoviruses are reduced by at least 1000 fold when liver cells are compared, thus supporting the phrase "significantly reduced tissue tropism for liver cells."

In the event the Examiner does not deem the term "significantly" to be sufficiently definite, applicants would consider deleting the word "significantly" from the claims. The phrase "reduced tissue tropism for liver cells" should indeed be definite and the Examiner is invited to contact the applicants' undersigned attorney in the event the suggested amendment would resolve the issue.

Accordingly, reconsideration and withdrawal of the rejections of claims 2, 25, 37-40 and 42 are requested.

Claim 37

Claim 37 stands rejected under 35 U.S.C. § 112, second paragraph, as being assertedly incomplete for omitting essential steps, resulting in a gap between the steps. Applicants propose to amend to claim 37 as set forth herein, and in view of the amendment respectfully traverse the rejection.

Applicants propose to amend claim 37 to include additional steps in the method. In view of the proposed amendment to claim 37 and the data supporting the significantly reduced tissue tropism of the adenovirus capsid, reconsideration and withdrawal of the rejection of claim 37 is requested.

Claim 10

Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claim 10 has been cancelled rendering the rejection moot.

IV. 35 U.S.C. § 112, First Paragraph

Claims 2, 38-40, 44, 45, 51, 52 and 54-57

Claims 2, 38-40, 44, 45, 51, 52 and 54-57 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants propose to amend claims 2, 38-40, 44, 45, 51, 52 and 54-57, and in view of the amendments respectfully traverse the rejections.

Specifically, it was thought that the scope of the claimed invention was very broad and that the few examples provided in the specification were not sufficient to represent the full scope of the claimed invention. The proposed amendments replace the phrase "gene delivery vehicle" with "recombinant adenovirus." Since the specification clearly provides support for the recombinant adenovirus with reduced tissue tropism for liver cells as recited in claims 2 and 38-40 (*e.g.*, Table II, top line) and the recombinant adenovirus with an increased tissue tropism for endothelial cells as recited in claims 44, 45, 51, 52 and 54-57 (*e.g.*, Figure 7A), reconsideration and withdrawal of the rejections are requested.

Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58

Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification assertedly does not reasonably provide enablement for any gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells, increased tropism for endothelial cells, or with a significantly reduced tissue tropism for liver cells for *in vitro* or *in vivo* gene delivery. Applicants have cancelled claims 1, 4-14, 16-18, 20, 24, 26, 41 and 43 rendering the rejection of these claims moot, propose to amend claims 2, 19, 38-40, 42, and 44-57, and in view of the proposed amendments respectfully traverse the rejections.

As proposed to be amended, claims 2, 38-40, 42 and 44-57 are directed to recombinant adenoviruses and not to any gene delivery vehicle. Since the application provides support for a cell that produces a recombinant adenovirus with a tropism for smooth muscle cells as recited in claim 19, a recombinant adenovirus with an increased tropism for endothelial cells when compared to wild-type virus as recited in claims 44-57, an adenovirus capsid having an increased tissue tropism for endothelial cells as recited in claim 58, an adenovirus capsid with a reduced

tissue tropism for liver cells as recited in claim 25, a method of reducing a tissue tropism of an adenovirus capsid for liver cells as recited in claim 37, and a recombinant adenovirus with a reduced tissue tropism for liver cells as recited in claims 2, 38-40 and 42, the claims are enabled. Accordingly, reconsideration and withdrawal of the rejections are requested.

Claim 10

Claim 10 also stands rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which assertedly was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors has possession of the claimed invention. Claim 10 has been cancelled rendering the rejection moot.

V. 35 U.S.C. § 102(b)

Claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41

Claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Stevenson et al. Claims 1, 4-8, 11-14, 16, 17, 24 and 41 have been cancelled making the rejections of the claims moot. Applicants propose to amend claim 19 to include the subject matter of claim 20, which was not rejected as being anticipated. Withdrawal of the rejection of claim 19 is thus requested.

Claims 1, 4-8, 10-14, 16, 17, 19, 24 and 41

Claims 1, 4-8, 10-14, 16, 17, 19, 24 and 41 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Wickham et al. Claims 1, 4-8, 10-14, 16, 17, 24 and 41 have been cancelled rendering the rejections of these claims moot. Applicants propose to amend claim 19 to include the limitations of claim 20, which was deemed not anticipated by Wickham et al. Accordingly, withdrawal of the rejection of claim 19 is requested.

VI. 35 U.S.C. § 103(a)

Claims 1, 4-14, 17-19, 24, 26 and 43

Claims 1, 4-14, 17-19, 24, 26 and 43 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Wickham et al. in view of Stevenson et al. and Woo et al.

Claims 1, 4-14, 17, 18, 24, 26 and 43 have been cancelled rendering the rejections of these claims moot. Further, Applicants propose to amend claim 19 to include the limitations of claim 20, which was not rejected as being obvious. In view of the proposed amendment of claim 19 to include the subject matter of claim 20, withdrawal of the rejection of claim 19 is requested.

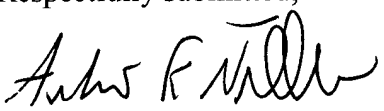
ENTRY OF AMENDMENTS

The proposed amendments should be entered because they are supported by the as-filed specification and drawings and do not add any new matter to the specification. Further, the amendments should not raise new issues or require a further search. Since the amendments comply with requirements to form set forth in the Final Office Action, and further place the application in condition for allowance, they should be entered. If the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

CONCLUSION

In view of the proposed amendments and remarks presented herein, applicants respectfully submit that the amended claims define patentable subject matter. If questions remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Date: September 23, 2002
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VERSION WITH MARKINGS TO SHOWN CHANGES MADE

2. (Thrice amended) A [gene delivery vehicle] recombinant adenovirus with a significantly reduced tissue tropism for liver cells.

19. (Four times amended) A cell for producing a [gene delivery vehicle] recombinant adenovirus having a tissue tropism for smooth muscle cells, said cell comprising:
means for the assembly of [gene delivery vectors] said recombinant adenovirus wherein said means includes at least one adenovirus nucleic acid for the production of an adenoviral fiber protein, wherein said adenoviral fiber protein comprises at least a tissue tropism determining fragment of a subgroup B adenoviral fiber protein and wherein said cell is of PER.C6 (ECACC deposit number 96022940) origin.

25. (Four times amended) An adenovirus capsid with a [significantly] reduced tissue tropism for liver cells wherein said adenovirus capsid comprises proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is of subgroup B adenovirus origin.

37. (Four times amended) A method of reducing [an adenovirus capsid of] a tissue tropism of an adenovirus capsid for liver cells, said method comprising: [incorporating a fragment of a fiber protein of adenovirus 16 in an adenovirus capsid therefor.]

i) exchanging a first nucleic acid encoding the tissue-tropism determining fragment of a fiber protein for a second nucleic acid encoding the tissue-tropism determining fragment of a fiber protein of adenovirus 16;

ii) introducing the resulting nucleic acid from step i) into a cell capable of producing said adenovirus capsid; and

iii) allowing said cell to produce said adenovirus capsid in a suitable medium.

38. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 2 wherein said tissue tropism is [being] provided by a virus capsid.

39. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 38, wherein said virus capsid comprises protein fragments from at least two different viruses.

40. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 39, wherein at least one of said viruses is an adenovirus.

42. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 40 wherein at least one of said protein fragments comprises a tissue tropism determining fragment of a fiber protein from a subgroup B adenovirus.

44. (Twice Amended) A [gene delivery vehicle] recombinant adenovirus comprising increased tissue tropism for endothelial cells when compared to other [gene delivery vehicles] recombinant adenovirus, wherein said tissue tropism is [being] provided by a virus capsid and wherein said virus capsid comprises protein fragments from at least two different viruses.

45. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein at least one of said viruses is an adenovirus.

46. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim [44] 45 wherein at least one of said viruses is a subgroup B adenovirus.

47. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein at least one of said protein fragments comprises a tissue tropism determining fragment of a fiber protein of subgroup B adenovirus origin.

48. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim [44] 46 wherein said subgroup B adenovirus is adenovirus 16.

49. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein said protein fragments are [not from an adenovirus of subgroup B and are] of adenovirus [of] subgroup C origin.

50. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein said virus capsid comprises protein fragments from at least two different viruses and wherein said protein fragments are [not from an adenovirus of subgroup B and are] from an adenovirus of subgroup C.

51. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 [wherein] further comprising an adenoviral nucleic acid.

52. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 51 wherein said adenoviral nucleic acid comprises sequences from at least two different adenoviruses.

53. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 51 wherein said adenoviral nucleic acid comprises at least one sequence encoding a fiber protein comprising a tissue tropism determining fragment of a subgroup B adenovirus fiber protein.

54. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 51 wherein said adenoviral nucleic acid is modified such that the capacity of said adenoviral nucleic acid to replicate in a target cell has been reduced or disabled.

55. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44, [further comprising] wherein said recombinant adenovirus comprises a minimal adenovirus vector or an Ad/AAV chimaeric vector.

56. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 further comprising at least one non-adenoviral nucleic acid.

57. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 56 wherein at least one of said non-adenoviral nucleic acids is a gene selected from the group of genes encoding a protein selected from the group consisting of: an apolipoprotein, a nitric oxide synthase, a herpes simplex virus thymidine kinase, an interleukin-3, an interleukin-1α, an [(anti)] angiogenesis protein, an anti-angiogenesis protein, an anti-proliferation protein, a smooth muscle cell anti-migration protein, a vascular endothelial growth factor [(VGEF)], a basic fibroblast growth factor, a hypoxia inducible factor 1α [(HIF-1α)] and a PAI-1.